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The Synthesis and Cycloaddition Reactions of 3-Azabicyclo[3.1.0]hex-2-ene 3-oxide and 3-Azabicyclo[3.2.0]hept-2-ene 3-oxide. Highly Strained Bicyclic Nitrones

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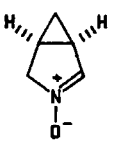
Abstract - The synthesis of two strained bicyclic nitrones is described. Subsequent cycloadditions demonstrated a high degree of regiochemical and stereochemical control.

The [3+2] cycloaddition of nitrones with various dipolarophiles has led to the synthesis of nitrogen containing natural products. Nitrones have been the subject of numerous reviews.[1-6] We wish to report the synthesis and cycloaddition reactions of the strained bicyclic nitrones **1** and **2** which have served as precursors for our work on the synthesis of 1,4- and 1,5-dienes.[7]



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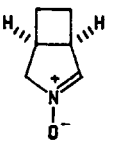
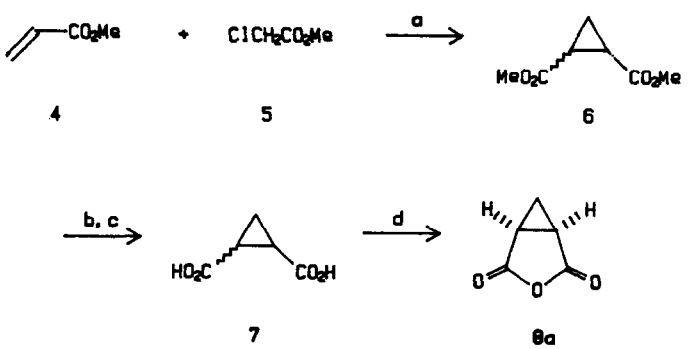


2

3

The synthesis of these nitrones is shown in Schemes I-III.

Scheme I: Entry Into The Bicyclo[3.1.0]-hexane Ring System.

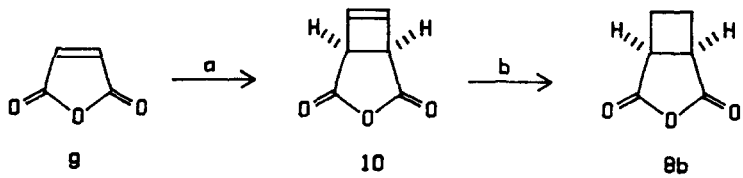


4 **5** **6**

7 **8a**

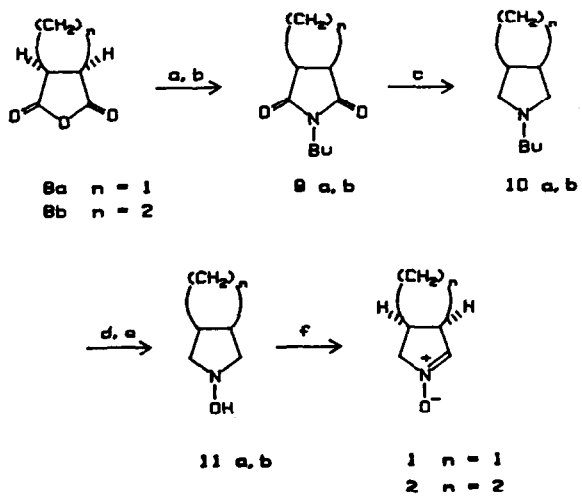
Reagents: a. NaH; b. NaOH; c. HCl; d. Ac_2O.

Scheme II: Entry Into The Bicyclo[3.2.0]-heptane Ring System.



Reagents: a. $HC \equiv CH/h\nu$; b. H_2/10% Pd-C.

Scheme III.



Reagents: a. $BuNH_2$; b. Ac_2O; c. $LiAlH_4$; d. MCPBA; e. 170°; f. HgO.

The synthesis of the nitrone **1** begins with a based induced condensation of methyl chloroacetate with methyl acrylate to afford a mixture of the cis- and trans-cyclopropyl diesters **6** in 65% yield.[8] Saponification and subsequent acidification provided the corresponding diacid in 80% yield, also as a mixture of cis- and trans-isomers.[9,10] Treatment of the diacid mixture with acetic anhydride under equilibrating conditions gave the cis-bicyclic anhydride **8a** in 80% yield.

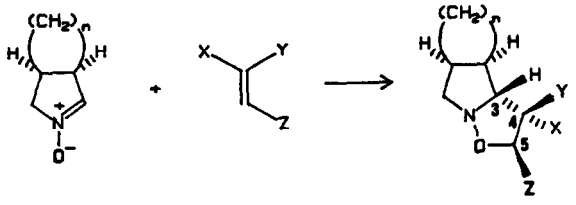
Entry into the bicyclo[3.2.0]heptane system present in nitrone **2** was easily accomplished by the photolysis of maleic anhydride with acetylene,[11] using a Hanovia 450W photochemical lamp, to give the bicyclic anhydride in 56% yield. Hydrogenation of this adduct with 10% palladium-on-carbon afforded the saturated anhydride **8b** in 96% yield.

From this point, the synthesis of the two nitrones utilized the same route, as seen in Scheme III. The anhydrides were converted to the corresponding N-butyl imides by treatment with N-butyl amine at 175°, followed by ring closure of the intermediate amido acid with acetic anhydride at 200°in 80 and 90% yield for the 5,3- and 5,4-bicyclic imides, respectively.

Reduction of the imides with lithium aluminum hydride[12] gave the amines **10a** and **10b** in 90 and 92% yield, respectively. Oxidation with MCPBA followed by a Cope elimination afforded the N-hydroxylamines **11a** and **11b** in 88 and 84% yield. These were easily converted to the target nitrones **1** and **2** by oxidation with yellow mercuric oxide.

The bicyclic nitrones, **1** and **2**, were allowed to react with several representative olefins to determine if the cycloadditions occurred with the same regiochemical and stereochemical preferences as observed for the prviously studied nitrone **3**.[13,14] These reactions are summarized in Table 1.

Table 1



Adduct	n	X	Y	Z	Conditions[a]	Yield[b]
12	1	H	H	Ph	A	75%[c]
13	1	H	H	Bu	B	65%
14	2	H	H	Ph	C	84%[d]
15	2	H	H	Et	D	77%
16	2	H	H	Bu	C	82%
17	2	H	H	$(CH_2)_4$-OBz	E	64%
18	2	CO_2Me	H	Me	F	85%

[a]Reaction Conditions: A, 80°/Benzene; B, 80°/benzene/sealed tube; C, 110°/toluene; D, 110°/toluene/sealed tube; E. 80°/toluene/45,000 psi; F, 25°/benzene. [b]isolated yields. [c]The 75% yield of product consists of a 92:8 separable mixture of the exo adduct **12** and its corresponding endo isomer, in which the stereochemistry of Z is α. [d]The 84% yield of product consists of a 97:3 separable mixture of the exo adduct **14** and its endo isomer, in which the stereochemistry of Z is α.

The regiochemical and stereochemical outcome of the cycloaddition reactions of nitrones such as **3** have been extensively studied. Several generalizations can be made from these investigations. For monosubstituted dipolarophiles, where Z is aryl or alkyl, 5-substituted isoxazolidines are regiospecifically formed.[15,16] With highly electron deficient olefins, a preference is seen for the formation of 4-substituted isoxazolidines. Methyl crotonate adds regiospecifically, giving 5-methyl-4-carbomethoxyl substituted isoxazolidines.[17] The cycloaddition reaction can proceed via an exo or an endo transition state leading to two possible stereoisomeric products. When there is an alkyl substituent on the monosubstituted dipolarophile, the exo transition state (ie. with regard to this substituent) is favored due to

unfavorable steric interactions that arise in the endo transition state.[1,16] An analysis of NMR chemical shift data and coupling constants suggests that the adducts obtained from **1** and **2** were formed with the expected stereochemistry and regiochemistry as depicted in Table 1. The most important feature of these cycloadditions, for our synthetic strategy, was that the dipolarophile specifically added from the α-face of the nitrones, presumably due to steric hinderance of the β-face by the cyclobutane ring system. Double irradiation of the protons in the 4-position of the isoxazolidine ring simplified the pattern assigned to the 3-proton to a singlet for all the adducts synthesized, (ie. **12-18**). The lack of vicinal coupling between the 3-proton and the cyclopropyl (or cyclobutyl) bridgehead proton could only be observed if the cycloaddition occurred from the α-face resulting in an approximately 90°dihedral angle between these protons as determined either by inspection of Dreiding molecular models or MM2 calculations.[18] Vicinal coupling would be expected if attack from the β-face had occurred. It is this α-face selectivity that serves as a cornerstone for our projected, stereoselective synthesis of 1,4- and 1,5-dienes.[7]

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